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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/058,292 | 01/30/2002 | James L. Hartley | 0942.285000H/RWE/BJD | 3058 |

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| EXAMINER | |
|---|---|
| AKHAVAN, RAMIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 05/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/058,292 | HARTLEY ET AL. | |
| | Examiner | Art Unit | |
| | Ramin (Ray) Akhavan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *35-227* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *213-225* is/are allowed.

6)☒ Claim(s) *35-153,158-212,226 and 227* is/are rejected.

7)☒ Claim(s) *154-157* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



S1020

## DETAILED ACTION

Receipt is acknowledged of a response, filed 03/22/2005, amending claims (35, 60-65, 78, 99-101, 115, 135-137, 159, 170-175, 187 and 198-200). Claims 35-227 are currently pending, of which claims 151-157 and 213-225 were previously indicated as allowed. However, in light of the new grounds of rejection set forth below, allowance is withdrawn for claims 151-153. (Infra, Rejections Nos. 4 and 5).

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections maintained.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/22/2005 has been entered.

### *Claim Objections*

Claims 154-157 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Appropriate correction is required.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 57-58, 96-97, 132-133 and 196-197 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

This rejection is of record and repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. Each of the claims recite the limitation that the first or second gene, or portion thereof, is located "immediately adjacent" to a given recombination site (e.g. claims 57-58, 96-97, 132-133, 196-197). The term "immediately adjacent" is not defined in the specification and it is unclear the structural/functional requirements for satisfying this limitation. Does the term necessarily mean that the recombination site is "immediately adjacent" to the gene or portion thereof with no intervening nucleotides? Or can some unspecified number of nucleotides be present between the portion of the gene and the recombination site and still meet the limitation of being "immediately adjacent"? While it is understood that in making a similar rejection in the previous office action the examiner presented the phrase "immediately adjacent" to mean that there are no nucleotides between the different elements, this does not mean that the term is necessarily limited to this interpretation by the instant specification (e.g. see the New Matter rejection above) or prior art. The term "immediately adjacent" is not clearly defined in the prior art and is subjective.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that one of skill will readily understand that the term "immediately adjacent" means that the recombination sites and related genes have no intervening nucleotides between them. (Remarks, p. 42, ¶ 2). Furthermore, Applicant directs attention to Figures 8B, 8I and 8J for support of this assertion.

As stated below, the term "immediately adjacent" cannot be exclusively interpreted to mean that there are no intervening sequences between a recombination site and a related gene. (See, infra, § 112, ¶ 1 Rejection). Given a broad and reasonable interpretation of the limitation "immediately adjacent", one can interpret the term to mean that there are intervening sequences (e.g., unused restriction sites in a multiple cloning site), because it is impossible to deduce whether there are intervening sequences between the recombination sites and related genes as depicted in the Figures 8B, 8I and 8J. Without an actual sequence map of a given vector depicted in said figures, it is unclear whether intervening sequences occur. As noted below, the figures merely provide reference symbols (i.e., triangles) that mark where a recombination site occurs and the triangles appear next to demarcations for a gene (e.g., GST gene). The alternative interpretations stated above lead to distinct boundaries for invention, with respect to what constitutes "immediately adjacent". As such, the artisan is unable to determine the claims' metes and bounds.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**2. Claims 57-58, 96-97, 132-133 and 196-197 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The independent claims recite the limitation "immediately adjacent to". However, there is no literal support in the originally filed specification or claims for the cited phrase. Therefore, the term is impermissible NEW MATTER.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that the specification provides literal support for the limitation "immediately adjacent to" and further asserts that one of skill would readily understand that the limitation means that the recombination sites have no intervening nucleotides between them. Furthermore, Applicant directs attention to Example 6, as well as Figures 8B, 8I and 8J.

The limitation "immediately adjacent" is not defined in the specification and the plain meaning of the term is not automatically interpreted to mean that there are no intervening sequences. For example, if a sequence is inserted into a multiple cloning site, it is possible that the insert is *immediately adjacent* to a regulatory element but where there are intervening sequences (e.g., unused restriction sites).

Furthermore, Example 6 (directed to manipulation of the vector depicted in Figure 7C) and the vectors depicted in Figures 8B, 8I and 8J do little to provide support for the contention that there are no intervening sequences. Each of the vectors depicts recombination sites as referenced by symbols (e.g., triangles), which appear to be next to a gene. However, it is ambiguous as to whether there are intervening sequences between the marked location for a recombination site and the nearest gene, solely based on the schematic representations of the cited figures. The vector maps merely provide schematics without disclosing any information as to whether there are intervening sequences.

Moreover, without a sequence map for a given vector, it is impossible to deduce whether there are intervening sequences between a recombination site and a gene. In sum, there is no literal support for the limitation "immediately adjacent". Furthermore, whether Applicants have implicit support in lieu of explicit literal support is indeterminable, because the cited figures are ambiguous as to whether "immediately adjacent" encompasses a genus of sequences with a particular structural limitation. Therefore, for reasons of record and for reasons stated herein, this rejection is maintained.

## *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**3. Claims 35-71, 74-77, 158-180 and 183-186 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al (WO 93/19172, of record; see the entire application).**

This rejection is of record and repeated herein. A response to Applicant's argument is set forth immediately following the body of the rejection. To the extent that arguments made previously and incorporated by reference in the latest response are still applicable to the rejected claims, the examiner's arguments to rebut the previous arguments are incorporated herein by reference as well.

Johnson et al teach methods for producing members of specific binding pairs featuring the use of recombinant bacteriophage to display functional antibodies (e.g. scFv; see, for example, pages 19, 26-34, 46-47, 49 and 52). Their methods include a method of producing a nucleic acid molecule by providing a first nucleic acid molecule comprising a first portion of a gene and a recombination site, a second nucleic acid molecule comprising a second protein of a gene and a recombination site, mixing *in vitro* or *in vivo* the first and second nucleic acids with a recombination protein to recombine the first and second nucleic acids to form a third nucleic acid, thereby forming an operably linked and functional gene from the first and second portions of the gene. Johnson et al teach the recombination of immunoglobulin genes in a phage that expressed the recombined immunoglobulin genes by joining the recombined immunoglobulin with a promoter that causes the expression of the recombined immunoglobulin genes on the surface of the phage (e.g. pages 26-34). The gene may encode a selectable marker or a heterodimeric product (e.g. pages 32 and 47).

The first or second portion of the gene may be fragments of the gene and may comprise a promoter and may further be a PCR product (e.g. pages 32 and 52). The first and second portions of the gene may be located adjacent to the recombination site, and the first or second nucleic acid molecule may comprise a cloning site (e.g. pages 19, 26-27, 31-32 and 46). The first, second or third nucleic acid may be an expression vector and may be linear. The functional gene may be expressed in a host cell and may be selected (e.g. phage display). The host cell may be *E. coli* (e.g. pages 26-34). The recombination sites may be loxP sites or att sites. The recombination protein may be Cre, Int, IHF, Xis, Flp, gamma-delta, Tn3, Hin, Gin or Cin (e.g. pages 26-34).

Johnson et al teach that additional recombination sites may be present on the recombination substrates (e.g. pages 22-23). Johnson et al teach that the vector FdDOG-1 is derived from pUC19, which has multiple cloning sites.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. In sum, Applicant asserts that Johnson et al. do not enable *in vitro* recombination and thus is not a proper reference. (e.g., Remarks, p. 39, ¶ 1). Furthermore, Applicant contends that the level of skill in the art does not support the assertion that experimentation required to practice the methods of Johnson et al. *in vitro* would have been routine. In addition, Applicant asserts that Boyd et al. does not teach *in vitro* recombination between a first and second nucleic acid molecule, thus Boyd et al. does not further support that *in vitro* recombination would have been routine. In essence, Applicant's argument comes down to whether Johnson's disclosure for *in vitro* recombination is enabled, considering what was known in the art at the time of invention.

Recombination reactions conducted *in vitro* were well known and conditions for such reactions were routine in nature with minimal levels of difficulty. For example, Abremski et al. teach an *in vitro* method to carry out intermolecular recombination between two *loxP* sites. (e.g., Abremski et al. J. Biol. Chem. 1984; 259:1509-14; See, p. 1509, col. 2, ¶ 1; p. 1510, col. 1, ¶ 1; p. 1512, last ¶, bridging to p. 1513, col. 1). Furthermore, for *in vitro* recombination, Abremski et al. teaches that cofactors or accessory proteins are not required for efficient recombination. (e.g., p. 1513, col. 1, ¶ 1). It is noted that with respect to intermolecular recombination both Cre recombinase and Int, Xis and IHF as well as γδ resolvase all appear to act stoichiometrically during recombination. (e.g., p. 1513, col. 2, ¶ 4).

In other words, increased efficiency of recombination reactions concentrations for a given combination of components results from increasing concentrations. However, the salient point is that Abremski et al. set out the *in vitro* conditions necessary to effectuate site-specific recombination for a *Cre/lox* system. (e.g., p. 1510, col. 1, under *Assay for Recombination in Vitro*). Moreover, the reference teaches that *Cre* can carry intermolecular or intramolecular recombination between two *loxP* sites. (e.g., p. 1513, col. 1, first full ¶). Therefore, the relevant point is that there are two site-specific recombination sites, not that they are contained on the same or different nucleic acid molecules.

Additional *in vitro* site-specific recombination reactions are demonstrated to be routine in the art. Indeed, "The requirements of the *in-vitro* [recombination] reaction are very simple…". (See, Senecoff et al. J. Mol. Biol. 1988; 201; 405-421, at page 405, col. 2 middle, and p. 409, Figure 2; teaching a method for intermolecular *in vitro* recombination utilizing the FLP site-specific recombinase).

Clearly, the prior art teaches that *in vitro* intermolecular recombination reactions involve nothing more that routine practice. (Id., p. 410, Figure 3). Moreover, the various recombination systems (i.e., recombinase protein and cognate recombination sites) are extendable (i.e., interchangeable) in the context of targeted site-specific recombination between nucleic acid molecules in eukaryotes and prokaryotes. (Infra, Fukushige et al. 1992, p. 7908, col. 2, first ¶, under Discussion). Therefore, there is a level of interchangeability amongst the various site-specific recombination systems in the context of recombination reactions.

In view of the knowledge with respect to *in vitro* recombination reactions, the teachings of Boyd et al., contrary to Applicant's assertion, are relevant. As stated above in the body of the rejection, while there may have been some vagaries as to conditions for *in vitro* recombination, such experimentation would have been routine, as indicated by both the Johnson et al and Boyd et al references (e.g. Boyd et al teach that Cre-mediated recombination *in vitro* is efficient and Johnson teach a methodology that can be readily used to determine whether the desired recombination products are formed). Furthermore, as stated above, Abremski et al. and Senecoff et al. clearly demonstrate that *in vitro* recombination is routine, regardless of being intra- or inter-molecular.

It follows, Applicant's assertion that *in vitro* intermolecular recombination present difficulties that require significant undue experimentation is not supported by the teachings of the prior art as discussed in the foregoing. Therefore, where a reference teaches methods of site-specific recombination and explicitly teaches that recombination can occur *in vitro* and *in vivo*, in conjunction with the teachings in the prior art that indicate that factors, components, buffers, steps necessary for *in vitro* recombination reactions are merely routine, then said reference does

not necessarily have to disclose in detail that which is accepted as routine in the art. As outlined in the foregoing, *in vitro* recombination was well established and practiced in the prior art, regarding site-specific recombination systems. Thus, in light of the knowledge in the prior art, Johnson et al. must be deemed as providing a fully enabled disclosure, notwithstanding the reference's level of specificity for applications considered to be "very simple". (Supra, Senecoff et al. 1988). Put another way, if the public is already in possession of the particulars regarding *in vitro* intermolecular recombination, then it is not necessary for such particulars to be disclosed by Johnson et al.

4. **Claims 78, 81-85, 96-100, 102-108, 115, 118-121, 132-136, 138-141 and 151 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukushige et al. (PNAS 1992; 89: 7905-09; See whole document).**

This is a new ground of rejection. The limitation "first portion of" and "second portion of" (i.e., components) an antibiotic resistance gene is interpreted as broadly as reasonable to mean a first and second component of a selectable marker, where one component is the selectable marker and the second component is one that controls the expression of said marker (e.g., a promoter element). (e.g., Specification, p. 15, ll. 1, 20-24). The limitation "immediately adjacent" is ambiguous as stated above, but in the interest of advancing prosecution, the limitation is interpreted as broadly as reasonable to mean that their may be intervening nucleotide sequences between the related elements.

Fukushige et al. teach a method of site-specific intermolecular recombination where *Cre* recombinase facilitates recombination between plasmid pBS226 comprising a *loxP* site and a CMV promoter element, as presented in the following:

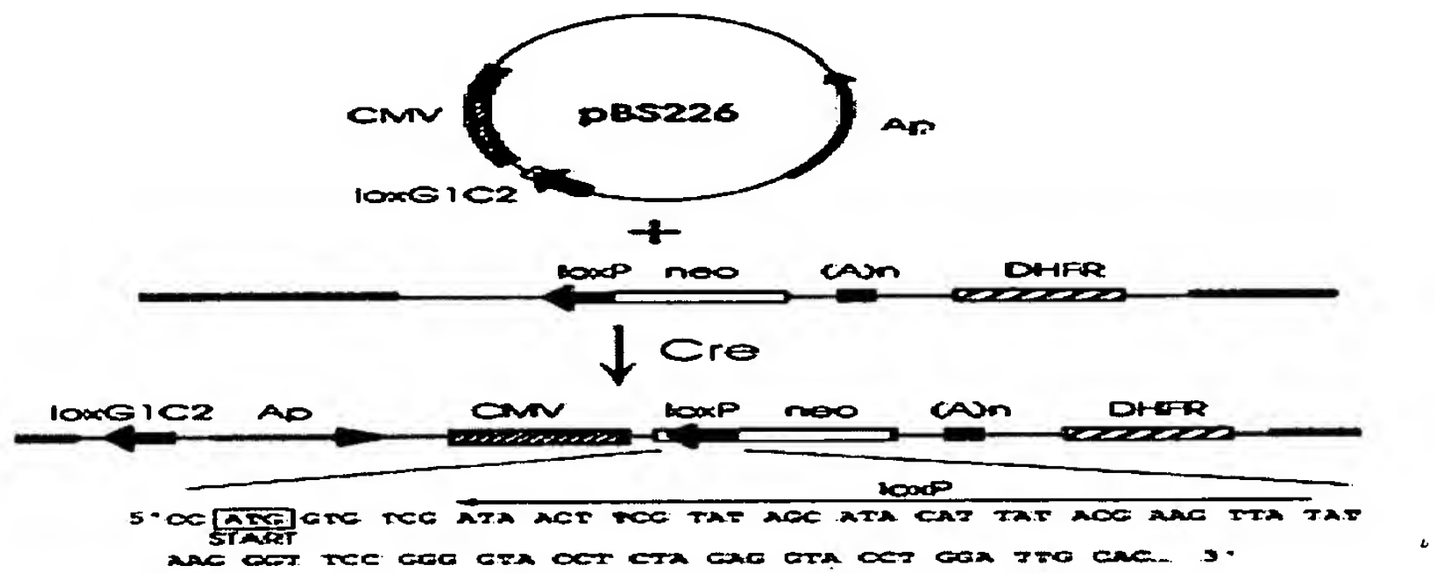


FIG. 2. Activation of a functional *lox–neo* gene by site-specific targeting. The circular targeting vector pBS226 and the chromosomal, nonfunctional *lox–neo* target of pSF14 are shown. Cre-catalyzed integration regenerates a functional *neo* gene. The resulting sequence is shown at the bottom.

(See, p. 7906, Fig. 2)

The second component is the selectable marker *neomycin*. As is clearly depicted in Figure 2, the mixture of pBS226 and the second nucleic acid molecule results in a third nucleic acid molecule where the CMV promoter controls expression of the selectable marker. Furthermore, the components of the vectors are produced by PCR amplification. (e.g., p. 7905, col. 2, under Materials and Methods). At least one of the nucleic acid molecules is an expression vector (i.e., the selectable marker is expressed in CHO cells). (e.g., p. 7907, Figure 3; p. 7908, Figure 4). Therefore, the reference anticipates the rejected claims.

***Claim Rejections - 35 USC § 103***

This application currently names joint inventors.

In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. **Claims 78-87, 96-111, 115-123, 132-141 and 151-153 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al. (PNAS 1992; 89: 7905-09; See whole document), in view of Johnson et al. (WO 93/19172, reference of record), and further in view of Lenski et al. (J. Bact. 1994; 176: 3140-47).**

The claims are interpreted consonant with the interpretations stated above. Furthermore, Fukushige et al. is applied here to the claims consonant to how the reference is applied above. (Supra, Rejection No. 4). Additional embodiments are directed to chloramphenicol as the selectable marker gene and *E. coli* as the host cell. Further embodiments are directed the λ Int/att recombination reaction (i.e., *att* recombination sites and λ Int recombinase).

Fukushige et al. does not explicitly teach utilization of chloramphenicol as a selectable marker. Furthermore, the constructs/nucleic acid molecules of Fukushige et al. are not reduced to practice for use in *E. coli*. Nor does Fukushige et al. teach the constructs to be used in a method utilizing a different site-specific recombination system (i.e., λ Int with *att* sites).

However, Fukushige et al. teach that bacterial geneticists commonly utilize site-specific recombination to integrate target DNA into the *E. coli* genome such as through λ Int/att site-specific recombination. (e.g., p. 7908, col. 2, ¶ 1). Importantly, the reference clearly implies that recombinases (thus in turn recombination sites) are extendable (thus interchangeable) between prokaryotes and eukaryotes. (Id.) Further, in implying such extendable recombinase systems, Fukushige et al. notes the Cre (loxP site), Int (attB site) and FLP (FRT site) are commonly available site-specific recombination systems. (Id.). Therefore, Fukushige et al. suggests that site-specific recombination via the various systems is interchangeable in prokaryotic and eukaryotic cells.

Furthermore, Fukushige et al. teach that cells transformed via targeted recombination reactions can be selected based on expression of a selectable marker. (e.g., p. 7908, col. 2, ¶ 20). In addition, Johnson et al. teach site-specific recombination in *E. coli* using various site-specific recombination sites and recombinase proteins. (Supra, Rejection No. 3). The teachings are in the context of *in vitro* recombination, but as discussed above, it would entail nothing more than routine practice to effectuate *in vivo* to *in vitro* intermolecular recombination. (See supra, Senecoff et al. 1988; Abremski et al. 1984; Boyd et al. 1993).

Therefore it would have been obvious to utilize the *Cre/loxP* recombination system of Fukushige et al. in an *E. coli* host cell so as to extend the range of organisms in which site-

specific recombination can be utilized. Furthermore, one of skill would recognize that given a different host cell is selected, an appropriate marker would also be selected from various antibiotic selectable markers that are commonly used in *E. coli* or bacterial cells, instead of a selectable marker used in mammalian cells.

For example, Lenski et al. teach several different antibiotic resistance genes that can be used as selection markers and to enhance bacterial fitness in one of the most widely studied and utilized bacterial species – *E. coli*. One would have been motivated to utilize different host cells so as to expand the range of organisms in which targeted recombination is utilized to obtain the benefit of cell transformation. One would have been motivated to utilize targeted recombination in *E. coli* to obtain the benefit of extending the range of organisms that can be manipulated. Given the level of skill in the art and the teachings cited herein, there would have been a reasonable expectation of success to adapt a site-specific recombination system to a different cell type, such as *E. coli*.

Moreover, substituting one selectable marker with another would entail nothing more than routine practice in the art of molecular biology. Therefore, one would have been motivated to substitute chloramphenicol or another antibiotic marker, to extend the range of selectable markers that can be used to select transformed bacterial (e.g., *E. coli*) cells. Given the level of skill in the art, substituting one antibiotic gene for another would entail nothing more than routine experimentation, thus there would be reasonable expectation of success. In addition, it would have been obvious to utilize a different combination of recombinase/recombination site.

As Fukushige et al. suggest and as Johnson et al. teach, multiple site-specific recombinases (along with their cognate recombination sites) can be used to effectuate targeted recombination. As stated above, Fukushige et al. explicitly note λ Int and teach that the recombination systems are extendable between eukaryotes and prokaryotes. And, Johnson et al. teach multiple combinations of recombinases/recombination sites utilized in targeted recombination. One would have been motivated to modify methods for targeted modification utilizing the λ Int/att combination of site-specific recombination to extend the range of different recombinases/sites that are available for targeted modification, for the benefit of introducing target DNA into a host organism. Given the level of skill in the art and the teachings cited herein, there would have been a reasonable expectation of success in modifying the methods as taught by Fukushige et al. to effectuate targeted recombination in *E. coli* using λ Int recombinase and *att* recombination sites. In summary, the additional embodiments are directed to a different selectable marker (chloramphenicol), a different cell (*E. coli*) and a different site-specific recombinase and recombination sites, i.e. site-specific recombination system (λ Int and *att* sites).

Given the knowledge in the art one of skill would recognize that said recombination systems are extendable from eukaryotes to prokaryotes. Further in selecting a host cell as the cell type to be modified through targeted recombination, one of skill would recognize that the appropriate selectable marker should be utilized. Therefore, the rejected claims are obvious over the cited art.

## *Conclusion*

Claims 213-225 are allowed. Claims 35-153, 158-212 and 226-227 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER